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April 28, 2011

Dr. Paul Anastas
Assistant Administrator for
Research and Development
1200 Pennsylvania Avenue
U.S. Environmental Protection Agency
Washington, DC 20004

RE: Withdrawal of the Noncancer IRIS Assessment of Methanol

Dear Dr. Anastas:

We are writing to request that you withdraw the noncancer IRIS assessment of methanol from its current public and peer review cycle. In our view, the current assessment is so fundamentally flawed that to proceed with peer review of the document would be meaningless, and in fact, counterproductive to good scientific process.

As you know, the current noncancer IRIS assessment is identical to the December, 2009 IRIS assessment of methanol released in January, 2010, except that the cancer sections of the assessment have been removed. Your staff has chosen to republish for public comment and peer review these identical pages without any alteration to reflect the changes in the scientific landscape for methanol in the intervening period. These changes require fundamental changes in the analysis of the methanol assessment which promise to radically alter the conclusions of the assessment, as we briefly outline below.

When asked why EPA has chosen to proceed in this manner, EPA staff have responded that this approach allows the Agency to avoid putting the assessment and the new science through the intra- and inter-agency review processes, thereby avoiding delay. The intent is to put the current draft (known by EPA staff to be flawed) through peer review, and THEN make the necessary changes to reflect the new science before publication. However admirable the goal of keeping to schedules may be, this desire to stay on schedule should not trump good scientific processes that are designed to assure the integrity of the resulting assessment.

We realize that your office often receives requests to delay or re-do your IRIS assessments, so let us explain why we believe that the developments since December 2009 fundamentally undermine the core elements of the current assessment and therefore necessitate a re-working NOW of the assessment rather than later after peer review:

The current draft assessment of noncancer effects of methanol bases its RfC and RfD conclusions on developmental effects in rodents AND makes these calculations on the basis of a PBPK model that DOES NOT take background levels of methanol into account.

The events since December 2009 that fundamentally challenge this approach to the assessment of noncancer effects are as follows:

- On April 8, 2011 the National Academy of Sciences released its report on the IRIS assessment of formaldehyde. Among the Academy's conclusions was the following: ***"The endogenous production of formaldehyde complicates the assessment of the risk associated with formaldehyde inhalation and remains an important uncertainty in assessing the additional dose received by inhalation, particularly at sites beyond the respiratory tract."*** Such endogenous and food sources of methanol also complicate an assessment of methanol. Human background levels appear to range from 0.4 and 4.0 mg/L. This range overlaps the proposed reference concentrations. For example, an 8 ounce glass of orange juice contains enough methanol to exceed the proposed reference concentration. Ignoring this problem of background is not a proper response from EPA any more in the case of methanol than it is in the case of formaldehyde.

- During 2010 and early 2011, the results of 4 years of research by the University of Toronto, instigated at EPA's suggestion, on the relevance of rodents for assessment of the health effects of methanol, were published, and subsequently brought to EPA's attention. These studies demonstrate that: methanol metabolism in rodents is different from primates (monkeys) and rabbits; that developmental toxicity from methanol is restricted to sensitive strains of rodents (no developmental effects in some strains of mice or in rabbits); that rodent metabolism of methanol by catalase produces reactive oxygen species (ROS) that play a large role in the developmental effects; and little ROS are produced in non-rodents, explaining why they are not sensitive to methanol developmental effects. EPA has no plans to point out these studies to the peer review panel, despite the fact that the proposed reference concentrations are based on rodent studies.

- More than a year ago, on March 15, 2010, the Methanol Institute submitted public comments on the current draft that presented information regarding both the relevance of the rodent data for assessment purposes for methanol and the need to take background levels of methanol into account. The Department of Defense submitted similar criticisms of the current draft during the Interagency Review process. **EPA staff have chosen not to respond in any way to either set of comments in the current draft, despite adequate time and opportunity.** EPA's proposed process now requires the Methanol Institute to re-submit these comments and to try to summarize them in 5 minutes before a peer review panel. Such a process may make sense for some issues, but not for such fundamental issues as the relevance of the rodent data to humans and the inadequacy of the PBPK model that was used by EPA staff to arrive at the proposed reference concentrations.

Your office's published process used for the Independent External Peer Review of IRIS files[1] has the following relevant statement of policy:

> *"The EPA takes its responsibility concerning peer review very seriously. EPA recognizes the importance of independent, external peer review in maintaining high standards for the quality of the science and technical products that EPA produces and sponsors. Peer review is an important component of the scientific process that provides a focused, objective evaluation of a draft product. The constructive criticisms, suggestions, and new ideas provided by the peer reviewers stimulate creative thought, and strengthen and confer credibility on the product. Comprehensive, objective peer reviews lead to good science and product acceptance within the scientific community. Thus, peer review insures that the Agency's scientific reports are held to the highest possible standards." (Page 1).*

[1] Policy and Procedures for Conducting IRIS Peer Reviews" (2009) (http://www.epa.gov/iris/pdfs/Policy_IRIS_Peer_Reviews.pdf).

As an example of how meaningless a peer review of the current draft assessment would be, particularly in light of the above policy of your office regarding peer review, the charge questions for the peer review ask: "Please comment on the scientific justification for the subtraction of background levels of methanol from the data in relation to the quantification of noncancer risks." The question is no longer should background levels be subtracted (the NAS has answered this question), but rather "How should the noncancer effects of methanol be quantified when background must be considered? How does one determine the contribution of background levels and exogenous levels to the total dose?" These are difficult questions to answer (which is probably the principal reason that EPA staff chose to subtract the background concentrations). This issue is made even more difficult in light of the Toronto research which shows that the rodent data probably do not provide a relevant starting point for such quantification.

EPA scientists should grapple with these challenging scientific issues BEFORE submitting the IRIS document for peer review, not AFTERWARDS. Otherwise, the peer review would be a worthless exercise. We note that these same issues regarding the assessment were raised in comments submitted by the Department of Defense on the 2009 draft and were ignored by EPA staff before releasing the 2009 draft for public review. This refusal to address legitimate and fundamental scientific comments and to proceed instead to peer review raises serious questions regarding EPA staff's commitment to "fix everything" after peer review and before the assessment becomes final.

We are therefore requesting that you withdraw the current noncancer assessment of methanol from the review cycle in order to allow the EPA staff to incorporate this new science and the new guidance from the Academy BEFORE resubmitting the assessment to the review cycle. We believe that the summary of the evidence provided in this letter should be sufficient for you, in consultation with your staff that are familiar with the details of what we present here, to decide to honor our request. However, should you wish to have a fuller presentation of the arguments for withdrawal, we suggest that you instruct your staff NOT to schedule the peer review of the methanol document as this time and then allow us and your staff to discuss these matters, hopefully in your presence, at the Listening Session now scheduled for May 26, 2011.

EPA staff have indicated to us that our March 15, 2010 and listening session comments on the cancer portion of the original draft assessment were very helpful and in part led to your staff's serious concerns regarding the Ramazzini Institute's methanol study. These concerns ultimately precipitated the Agency's decision to first put the entire methanol assessment on hold last June, and the more recent announcement that a full Pathology Working Group review of the methanol – and other studies – is now underway at the Italian lab, and that the cancer portion of the assessment remains on hold until this review has been completed. We certainly commend the EPA for taking these very appropriate steps to ensure that the best available science is used for the cancer portion of the assessment, and are suggesting here that no less an action is required to ensure the scientific integrity of the non-cancer portions of the methanol assessment.

Thank you for your attention to this important matter. We would like to meet with you to discuss this request in more detail and will call your office in a few days to seek a mutually satisfactory time for such a meeting.

Sincerely,

Gregory Dolan
Executive Director
Americas/Europe